The Disease of Opioid Addiction and Treatment with Buprenorphine

DMHA Symposium: Prescription Pain Medication & Heroin:

The Problem, Response, Remedies

April 14, 2010

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Substance Use Disorders Collectively Represent the #1 root cause of all Medical Morbidity and Mortality in the U.S.

Mokdad et al., JAMA, 2004

Opioid Addiction: How does it compare to all the others?

Data from National Houshold Survey on Drug Abuse (NHSDA) (2001 data)

Zacny et al. (2003). Drug and Alchohol Dependence

% population (12 or older) with Abuse/dependence	
Nicotine: ~ 34.8%	340,000 (number est. metro Indy)
Alcohol: 5.9 %	59,000
Marijuana: 1.5 %	10,500
Cocaine: 0.5	5000
Opioids (pills): 0.4%	4000
Heroin: 0.1%	1000

The modern explosion of opiate prescribing

Data from National Houshold Survey on Drug Abuse (NHSDA) (2001 data)

Zacny et al. (2003). Drug and Alchohol Dependence

MORPHINE

Year	ED mentions	Rx's (1000s)
1994	1099	1397
1998	1955	2190
2001	3403	3277

HYDROCODONE (e.g. Vicodin)

Year	ED mentions	Rx's (1000s)
1994	9320	39,218
1998	13,611	60,266
2001	21,567	83,213

OXYCODONE (e.g. oxycontin)

Year	ED mentions	Rx's (1000s)
1994	4069	11,742
1998	5211	16,194
2001	18,409	26,513

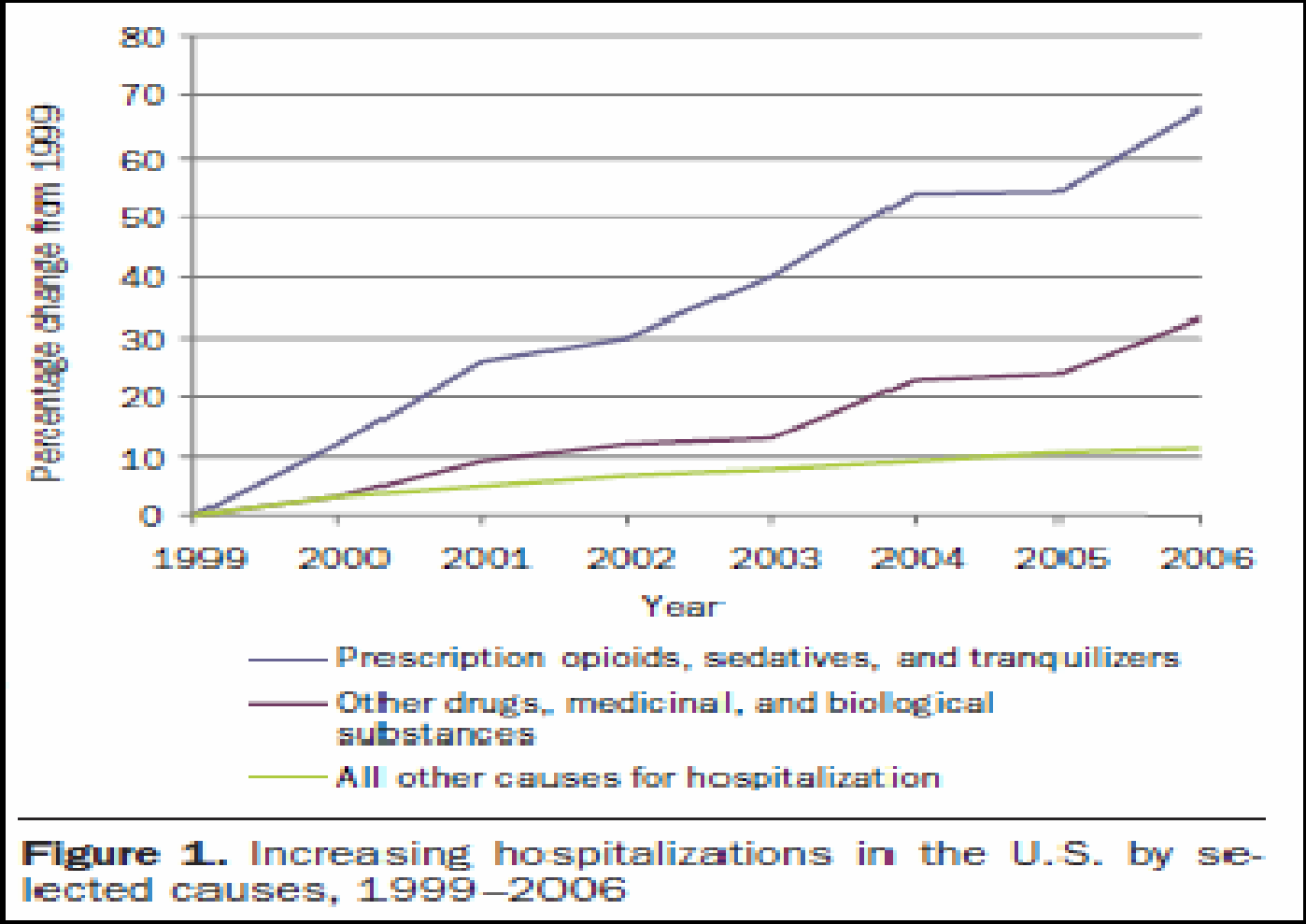


Figure 1. Increasing hospitalizations in the U.S. by selected causes, 1999–2006

U.S. poisoning hospitalizations:

	1999	2002	2004	2006
Opioids (not methadone):	7,742	12,946	15,766	17,545
Heroin:	3,971	4,572	3,961	4,858

Coben et al. (2010) American Journal of Preventative Medicine

Substance Dependence

Maladaptive pattern leading to clinically significant impairment or distress within a year including three or more of:

1. Tolerance
2. Withdrawal signs
3. Substance taken in larger amounts/longer period of time than intended
4. Persistent desire/unsuccessful efforts to quit/cut back
5. Great time spent acquiring or using substance
6. Social, occupational, recreational activities reduced or eliminated because of use
7. Use continues despite knowledge of medical or psychiatric problem resulting from use

Motivational

Injury

Nicotine, alcohol, cannabis, cocaine, amphetamine, opiates

Neurobiological Effects of Addictive Drugs

Cocaine	DA, 5HT, NE transporters	**DA**
	prefrontal cortex, striatum	**Nucleus Accumbens**
Amphetamine	‘’	‘’
Nicotine	Acetylcholine receptors	**DA**
	thalamus, striatum,frontal, parietal cortex	**Nucleus Accumbens**
Cannabis	Cannabinoid receptors	**DA**
	Cingulate, palladum, hippocampus, cerebellum	**Nucleus Accumbens**
Opiates	Mu and Kappa receptors	**DA**
	Neocortex, thalamus, striatum, cerebellum, PAG	**Nucleus Accumbens**
Alcohol	GABA and NMDA receptors	**DA**
	Everywhere!	**Nucleus Accumbens**

Opiates

Epidemiology USA Depenendence: 2.5% LT, 0.6 % point

Use of opiates for pain is one of the major miracles of modern medicine.

Heroin $50-200 K /kg
30-70% pure

Oxycontin:

	Rx	Street
10 mg	$1.25	$5-10
80 mg	$6.00	$65

Methadone

Fentanyl

Heroin

oxycodone

hydrocodone

Mainly Mu but Also kappa and delta opiate receptors

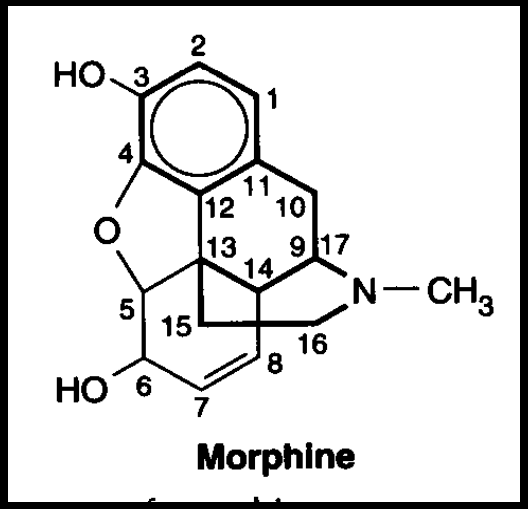
Endorphins
(18+)

Prodynorphin

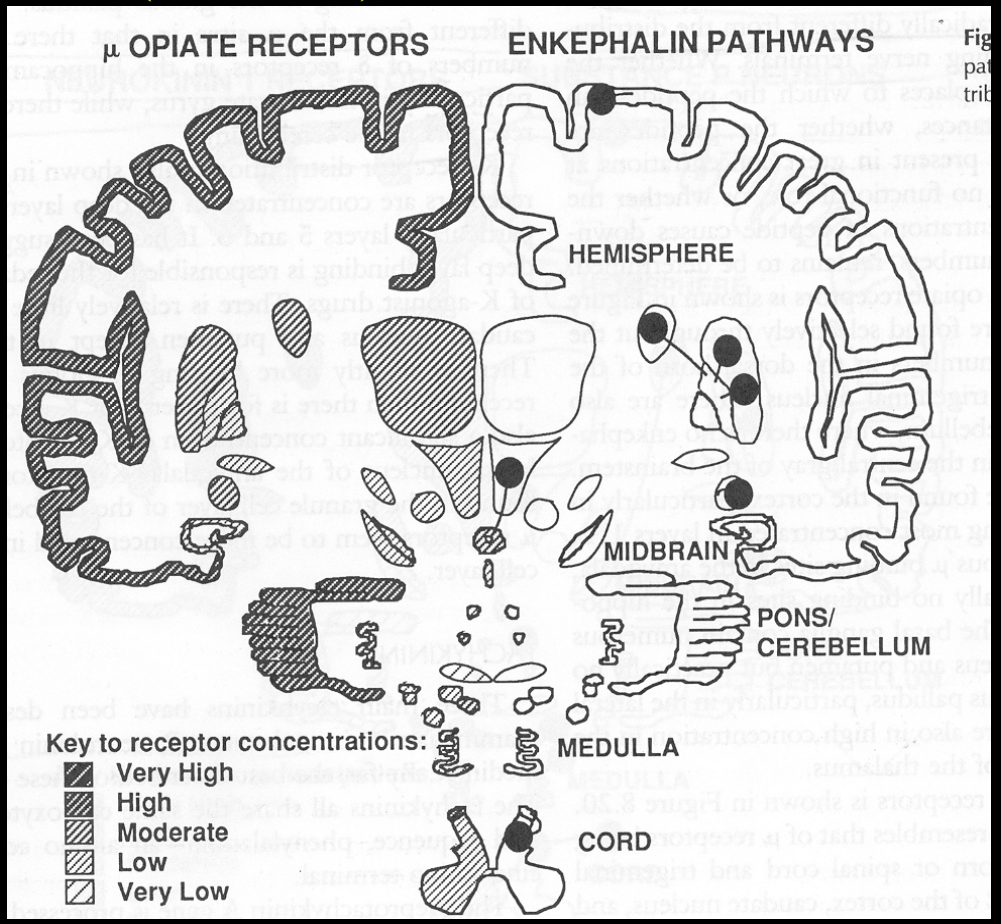
Proenkephalin

proopimelanocortin

striatum { Dynorphins enkephalins
(Substance P)

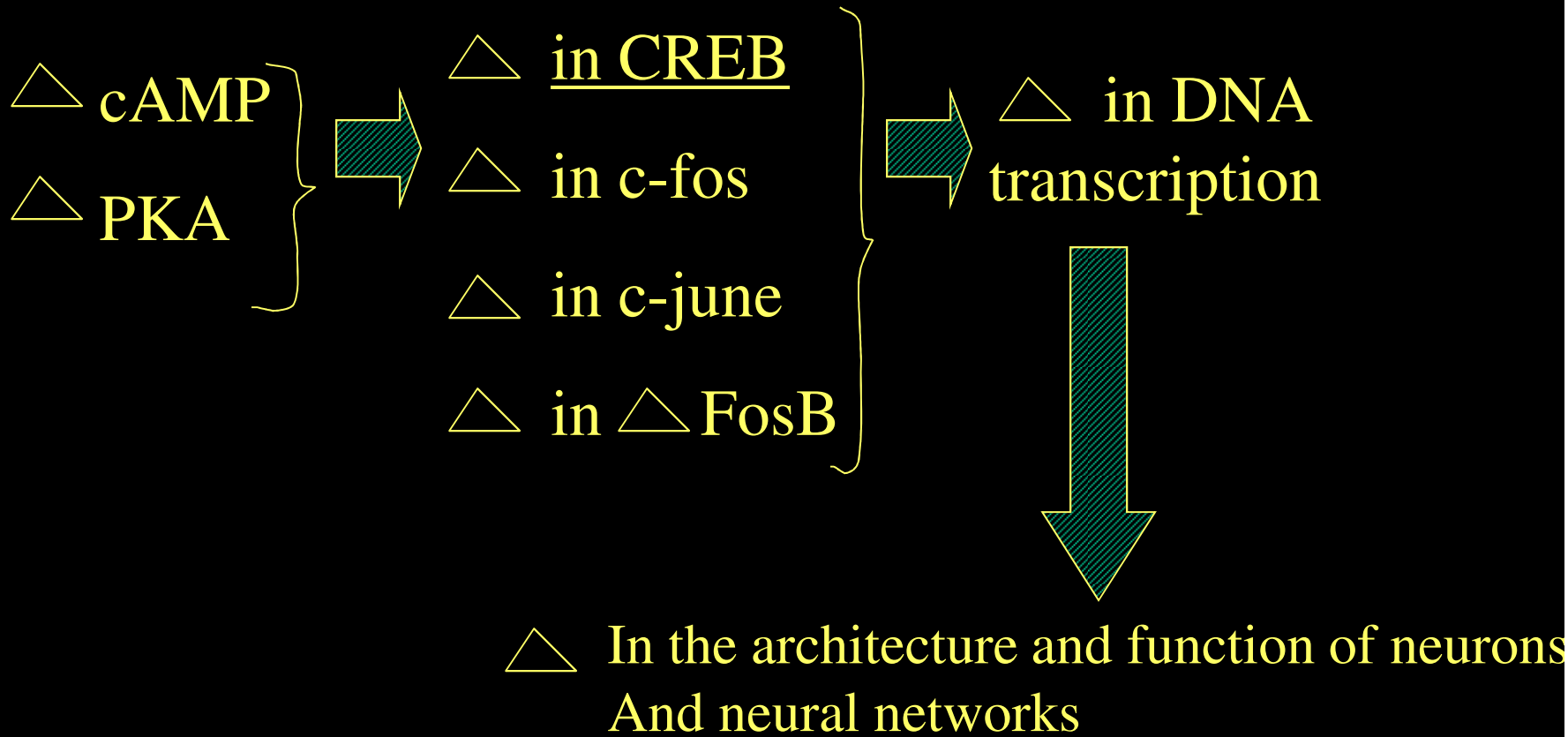


Morphine



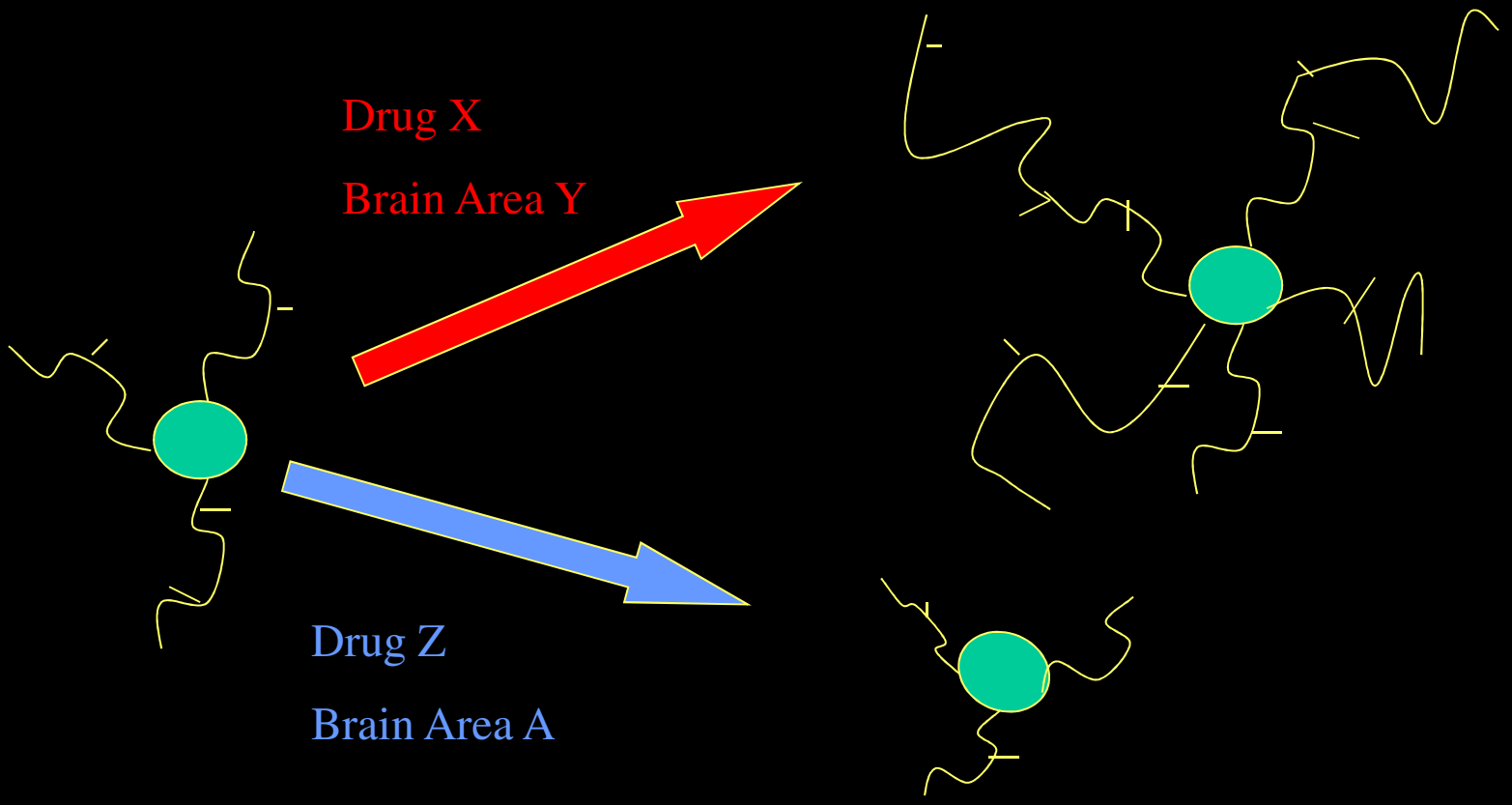
G protein mechanism…mu's inhibit Adenylate cyclase and activate K+ channels (out of the cell)

Acute and chronic administration of addictive drugs cause changes
in key intracellular proteins

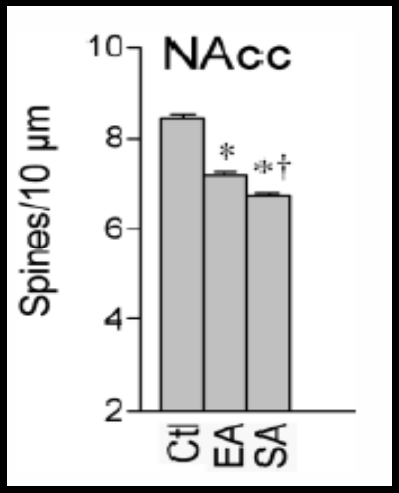


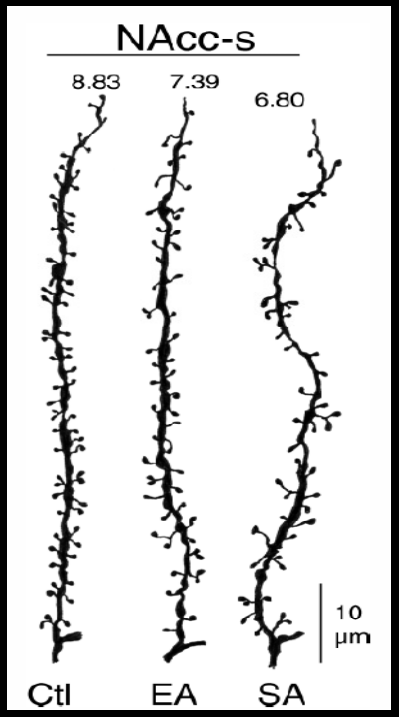
What exactly are these changes in neuronal architecture….

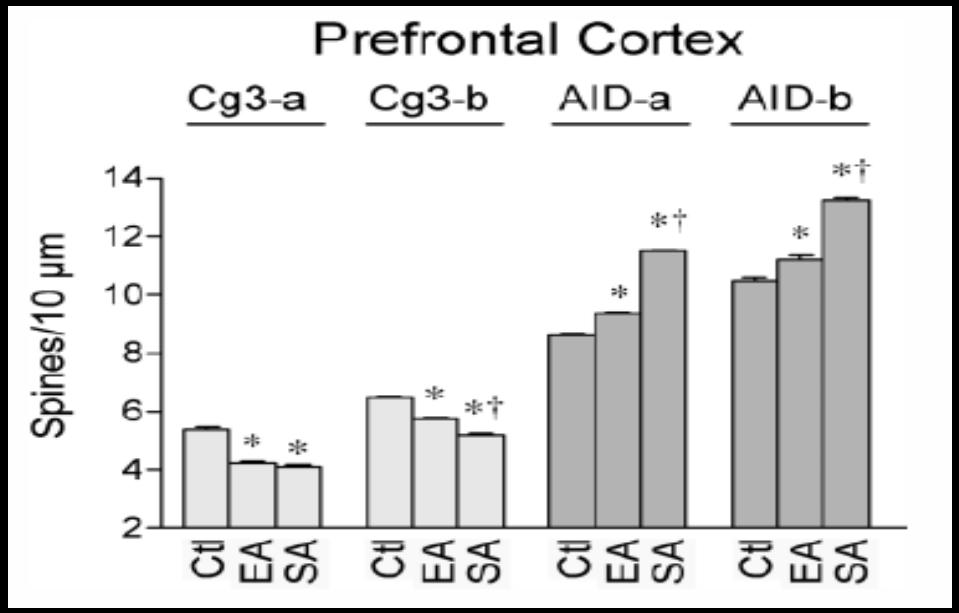
Changes in Neuronal Branching and synapatic spines in key circuits implicated in motivational control (NAC) and decision making (PFC).

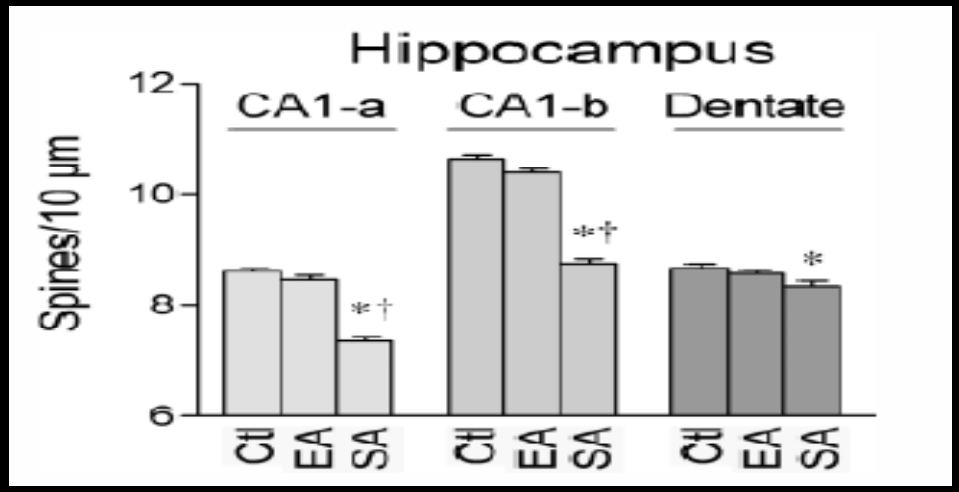


Neuronal changes due to chronic morphine administration



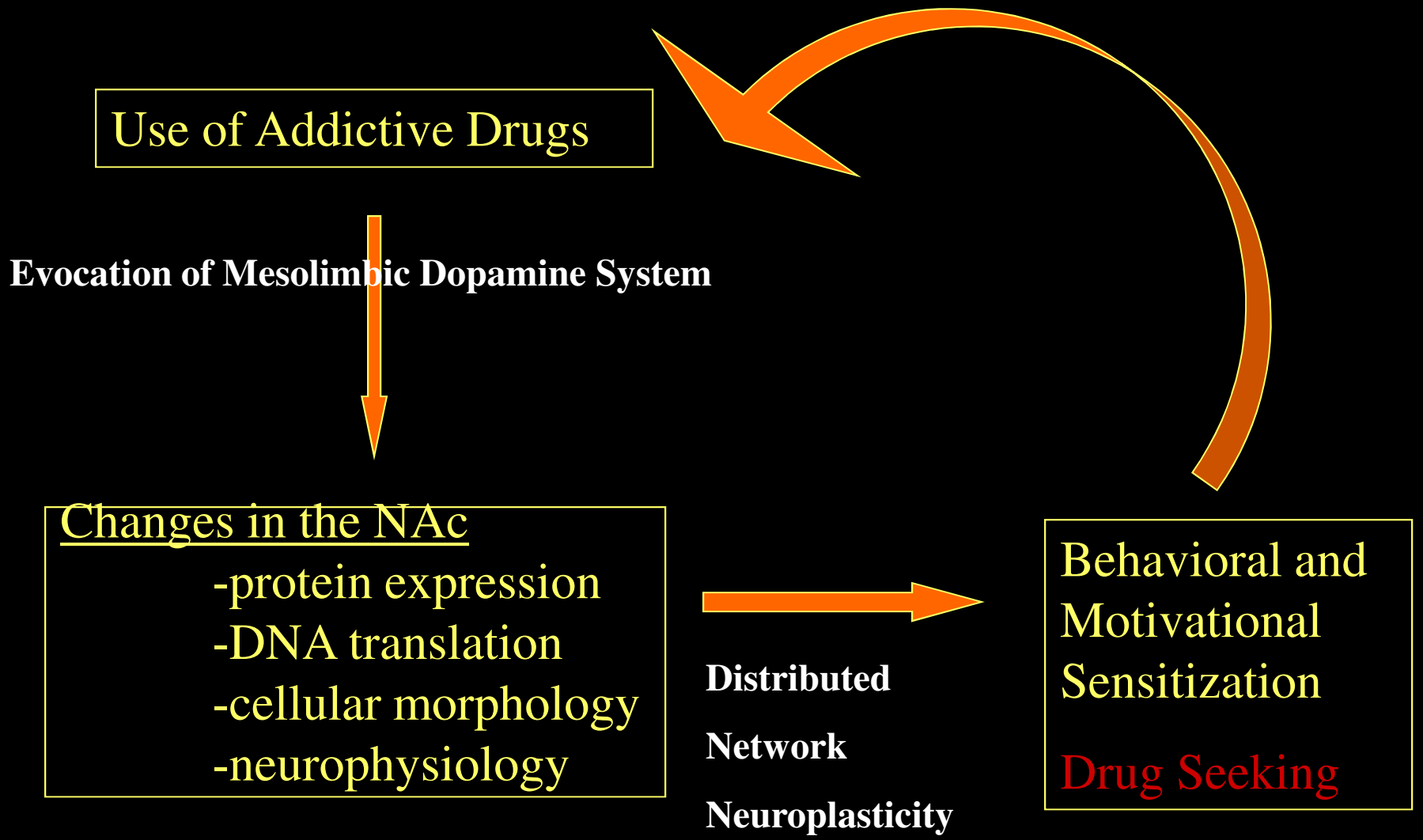






Robinson et al. (2002) Synapse

The Vicious Cycle of SUDs



(Nestler, 2001; Robinson, 2001; Thomas, 2001)

What are the Two Major Vulnerability Conditions for Addictions and how do we understand them neuroscientifically?

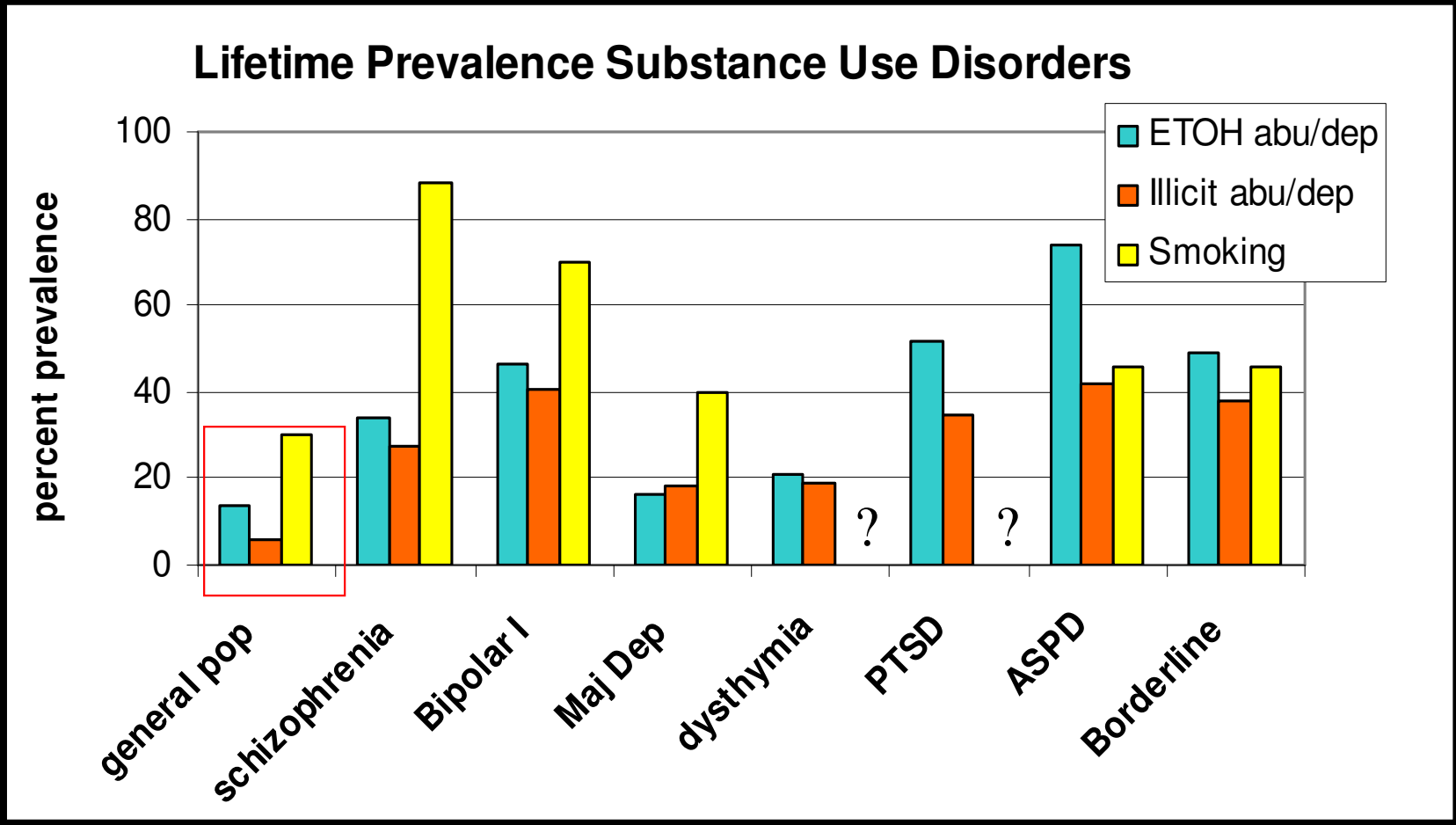
1. Presence of Mental illness

   (Chambers et al. Biological Psychiatry, 50: 3: 71-83, 2001)

2. Being an Adolescent/Young Adult

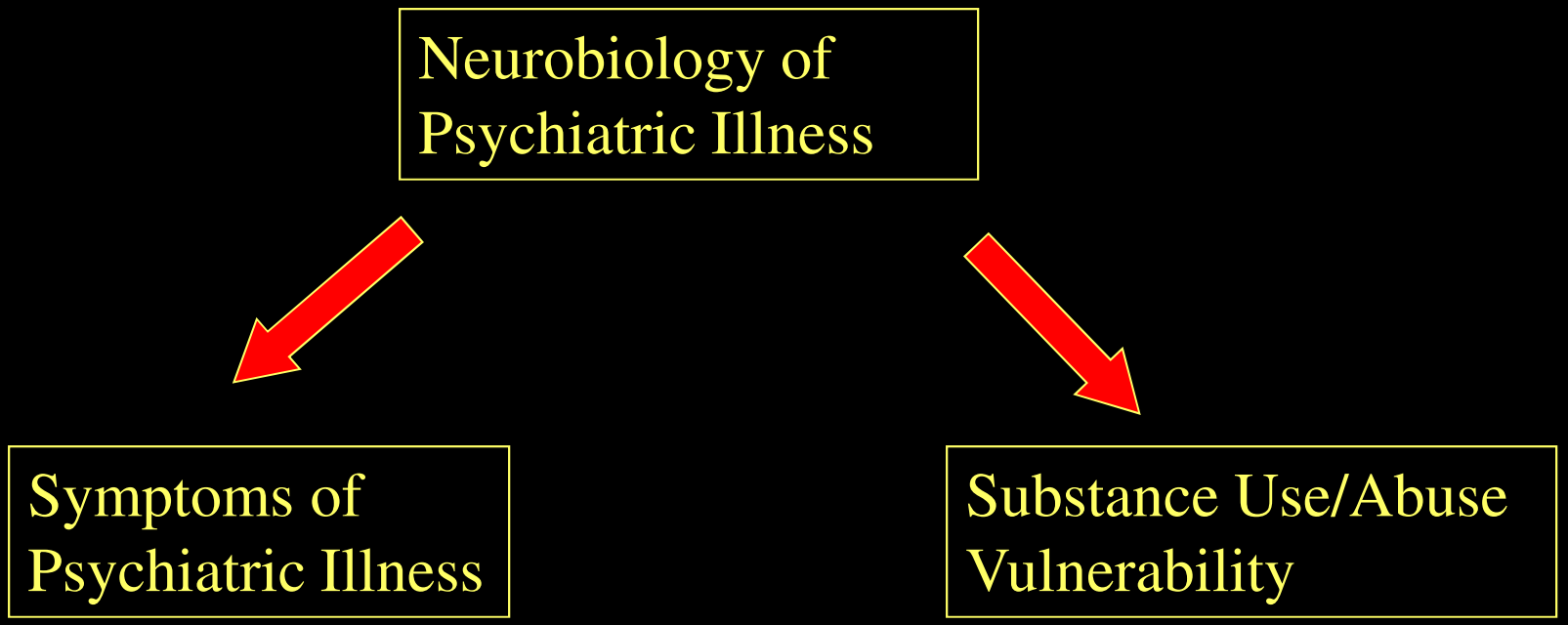
   (Chambers et al. American Journal of Psychiatry,160: 1041-1052, 2003)

Substance Use Disorders (SUDs) in Mental Illness



- General pop, schizophrenia, bipolar, unipolar, dysthymia (ECA data early 1980's) Regier et al.(JAMA,1990)
- PTSD (NCS data early 1990's) Kessler et al. (Arch. Gen Psy,1995)
- Borderline (1980's –1990s), Trull et al. (Clin Psy Rev, 2000)
- All smoking data (1980 local outpt study), Hughes et al. (Am J Psy,1986)

Integrative Circuit Hypothesis of Dual Diagnosis



Dual Diagnosis and Opiate Addiction

1. Co-morbidy of Opiate Addiction with another mental illness and/or other drug addiction is the rule and not the exception.

   - mental illnesses are biological vulnerability conditions for addictions
   - mental illnesses are vulnerability conditions for medical illness or surgical trauma that elicit over-prescribing practices of opiate medications
   - managed care + lack of health insurance + overspecialization of physicians + paucity of psychiatrists/addictionologists + inadequacy of addiction services.

2. 'Triple Diagnoses' (Opiate addiction/chronic pain/mental) illness is very common.

   - chronic pain conditions, what-ever the cause, are far more common in persons with mental illness (probably overlapping neurobiologies)
   - opiate addiction actually generates and perpetuates chronic pain in the long run

Data from Health Care for Communities survey (HCC) 1997-1998 (N=9279)

Sullivan et. al (2005) Pain

-3% of the general population without Cancer use opioids regularly.

- Among individuals receiving legally prescribed opioids, the rate of common mental health disorders (anxiety/depression) was 45%.

-of this 45%, less than 1/3 were being treated for their anxiety/depression with standard of care medicines

Data from the National Survey on Drug Use and Health

2002-2004 analysis of 91,823 people (representative sample of U.S. population)

Becker et al. (2008) Drug and Alchohol Dependence

In population subgroup with past year non-medical prescription opioid use compared to non-using subgroup (un-adjusted odds ratios):

un-insured:	2.4 x more likely
panic symptoms:	2.7 x more likely
depressive symptoms:	3.2 x more likely
manic symptoms:	3.9 x more likely
generalized anxiety :	3.0 x more likely
post-traumatic stress:	2.8 x more likely

alcohol abuse dependence:	12.7 x more likely
nicotine addiction:	4.2 x more likely***
other illicit drug use:	11.4 x more likely
non-medical use of other prescription drug:	35 x more likely

*** of those with abuse or dependence on prescription opioids, 75% were nicotine dependent

Treatments for Opiate Addiction

Abstinence-Oriented

Goal: achieve total recovery

- Individual Psychotherapy (e.g. Motivational Enhancement)
- Medication (e.g. Naltrexone)

Opiate Replacement:

Goals: Clinically Stabilize to prepare for or initiate Abstinance oriented and/or as a means of permanent harm reduction

- Methadone
- (LAAM)-gone because of bad side effect profile
- Buprenorphine (Suboxone)

Benefits of opiate replacement treatment

Unquestionably improves outcomes

IN EVERY SINGLE outcome measure that has been studied:

(e.g. improves financial stability, decreases legal involvement, decreases psychiatric and medical mobidity and mortality).

Limitations of Opiate replacement with Methadone

- There are not nearly enough treatment spots in proportion to need.
- Dangers of lethal OD, and other side effects.
- Methadone Treatment is extremely highly bureaucratically regulated and stigmatized, is incredibly intensive, and often/usually requires out of pocket payments from the patients.

Brief History of OMT

- 1964: Methadone is approved.
- 1974: Narcotic Treatment Act limits methadone treatment to specifically licensed Opioid Treatment Programs (OTPs).
- 1984: Naltrexone is approved, but has continued to be rarely used (approved in 1994 for alcohol addiction).
- 2000: Drug Addiction Treatment Act of 2000 (DATA 2000) expands the clinical context of medication-assisted opioid treatment.
- 2002: Tablet formulations of buprenorphine (Subutex®) and buprenorphine/naloxone (Suboxone®) were approved by the Food and Drug Administration (FDA).

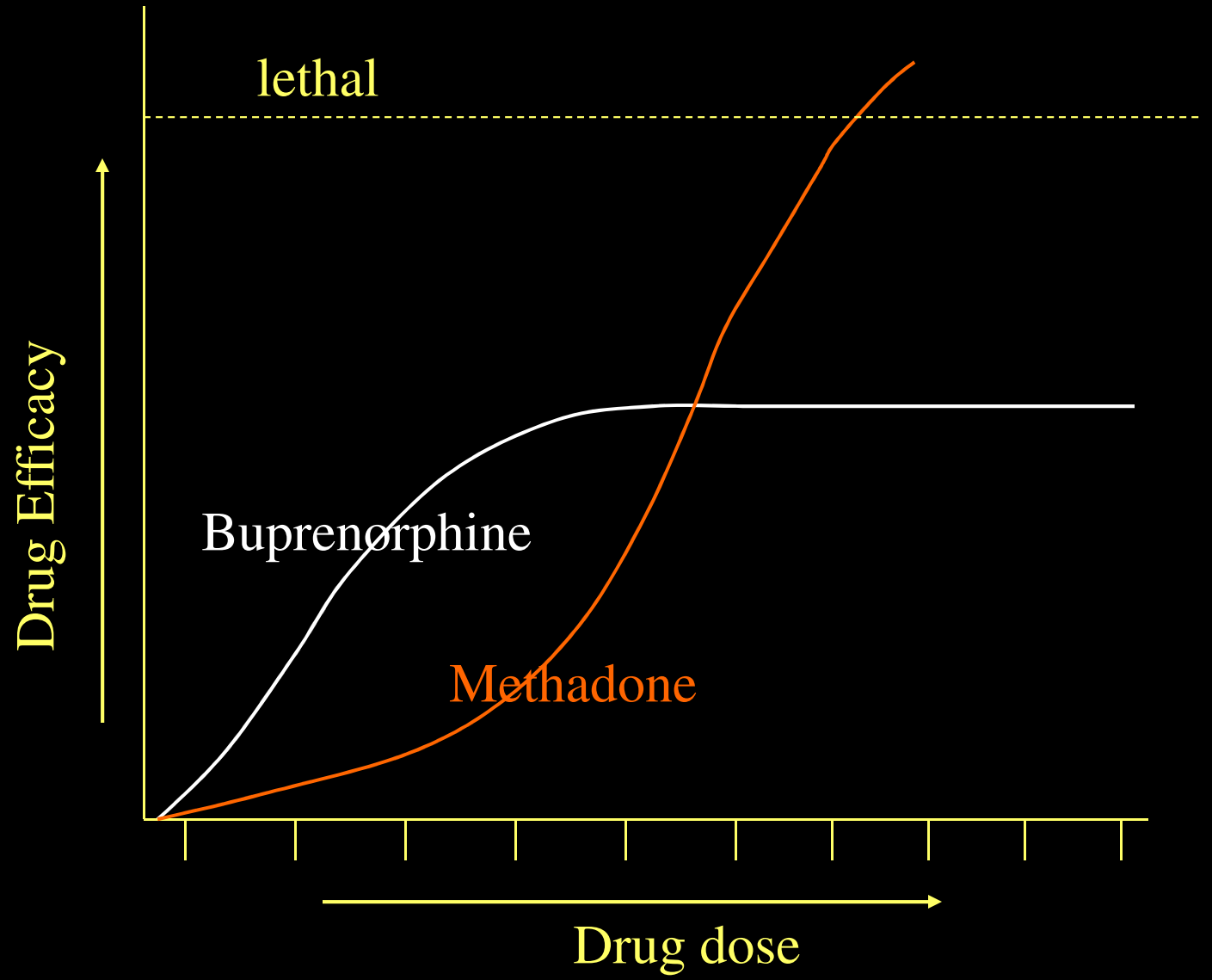
Drug Addiction Treatment Act of 2000 (DATA 2000)

- Expands treatment options to include both the general health care system and opioid treatment programs.
  - Expands number of available treatment slots
  - Allows opioid treatment in office settings (not just in approved Methadone programs)
  - Sets physician qualifications for prescribing the medication (makes it far easier for more docs to get involved).

Introduction to Buprenorphine (Suboxone)

Is it really special? YOU BETCHA!

1. It is a partial agonist at Mu receptors.
2. It has relatively high affinity at Mu receptors.
3. It has a relatively long half-life (~36 hrs)
4. Formulation with Naloxone (in Suboxone).


lethal
Drug Efficacy
Buprenorphine
Methadone
Drug dose

What about the '–oxone' in Suboxone?

Suboxone = buprenorphine + naloxone (8/2 mg ratio)

Subutex = buprenorhpine only

1. If you crush it up and inject it… the naloxone selective kicks in and will block the opiate and/or cause sudden withdrawal!
2. Can't really eat suboxone, poor GI absorpton:

   So… the formulation is a SL tablets.

Buprenorphine compared to Methadone: Advantages

1. Lack of bureaucratic regulation, restrictive/intensive treatment culture, relative ease with which treatment systems may get involved:

   --it can be used in treatment clinics that are interested or can devote energy to more than opiate addiction as the only problem (e.g. it is ideal for dual diagnosis capable treatment).

   -- does not engender policies that end up dismissing patients from treatment because they are too sick with other addictions

   -- does not engender treatment systems who's financial survival are dependent solely on number of methadone presriptions dispensed

   --it can be delivered on equal playing ground with other narcotics as they are chronically prescribed for chronic pain.

2. Safer Induction

3. Much lower risk of lethal overdose in combination with other opiates or other drugs

4. Actually blocks, rather than synergizes with other opiates

5. Not as much a risk of QT prolongation

6. May be safer in pregnant moms and young adults

7. Equivocal but probably will be more cost-effective in the long run.

Buprenorphine compared to Methadone: Disadvantages

There is likely a minor fraction of the opiate addicted population for which buprenorphine does not offer sufficient potency as an agonist to offer as effective a replacement treatment as methadone.

The degree to which this is true is unknown.

Buprenorphine/Suboxone

-Likley represents the future of opiate replacement therapy for most patients with opiate addiction.

-Will be key for the implementation of full-fledged dual diagnosis services, and/or treatment facilities that can focus on more than one type of addiction or mental helath condition.

-Like methadone, still needs to be imbedded in practices and treatment centers that offer: psychotherapeutic modalities of care for addictions, rigorous therapeutic drug testing approaches, and well-trained physician involvement (a current lack of these are serious barriers).

- Should be available in every single CMCH and State hospital in the state.

Thanks, Questions?

Lab for Translational Neuroscience
of
Dual Diagnosis & Development

Thankyou: NIDA, APA, NARSAD, Indiana DMHA, Indiana Department of Psychiatry

My participation in this conference is supported by Indiana DMHA.